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Diabetes and renal tubular cell apoptosis

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Abstract

Apoptosis contributes to the development of diabetic nephropathy, but the mechanism by which high glucose induces apoptosis is not fully understood. Apoptosis of tubular epithelial cells is a major feature of diabetic kidney disease, and hyperglycemia triggers the generation of free radicals and oxidant stress in tubular cells. Hyperglycemia and high glucose *in vitro* also lead to apoptosis, a form of programmed cell death. High glucose similar to those seen with hyperglycemia in people with diabetes mellitus, lead to accelerated apoptosis, a form of programmed cell death characterized by cell shrinkage, chromatin condensation and DNA fragmentation, in variety of cell types, including renal proximal tubular epithelial cells.

Key words: Tubular cells; Renal; Apoptosis; Diabetes

Core tip: Apoptosis contributes to the development of diabetic nephropathy, but the mechanism by which high glucose induces apoptosis is not fully understood. High glucose similar to those seen with hyperglycemia in people with diabetes mellitus, lead to accelerated apoptosis, a form of programmed cell death characterized by cell shrinkage, chromatin condensation and DNA fragmentation, in variety of cell types, including renal proximal tubular epithelial cells.

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DIABETES AND RENAL TUBULAR CELL APOPTOSIS

Diabetes is the leading cause of end-stage renal failure in most developed countries. Although vascular and glomerular injuries have been considered the main features of diabetic kidney diseases, tubular atrophy is also plays a major role in the disease[1]. Diabetes induces early signs of tubular dysfunction[2]. In addition, diabetic kidneys are particularly prone to acute tubular necrosis in diverse clinical situations, such as post-cardiac surgery[3]. Hyperglycemia, by itself, is an independent risk factor for acute tubular necrosis under these conditions[3]. Hyperglycemia triggers the generation of free radicals and oxidant stress in tubular cells[4,5]. Reactive oxygen species are considered to be important mediators for several biologic responses, including proliferation, extracellular matrix deposition and apoptosis[6]. Apoptosis, a form of programmed cell death characterized by cell shrinkage, chromatin condensation and DNA fragmentation, which, can be induced by various stimuli[7]. High glucose concentration promotes apoptosis in variety of cell types including proximal tubular epithelial cells[5,8]. The mechanism by which hyperglycemia leads to apoptosis is not completely understood.

A high glucose concentration of 30 mmol/L for 18-48 h has been shown to induce apoptotic changes in HK2 cells via an increase in oxidative stress[8]. Prolonged exposure (1-13 d) of proximal tubular epithelial cells to hyperglycemic environment has been shown to inhibit cell proliferation and induce growth arrest or cellular

apoptosis[8-12]. These cellular effects are caused by the activation of a network of intracellular signaling pathways and include the phosphatidylinostiol 3 kinase (PI3 kinase)/adams kara taylor (AKT) signaling pathway[13]. Activation of PI3 kinase and phosphorylation of serine/threonine kinase AKT/protein kinase B (PKB) by insulin, insulin like growth factors in human embryonic 293 (HEK-293) and HeLa cells lead to inactivation of tuberin by phosphorylating at Ser939, Ser1086/1088 and Thr1422[14,15]. In addition, phosphorylation of tuberin at Ser939 and Thr1422 in response to PDGF and insulin stimulation in a PI3K-dependent manner has been reported in NIH-3T3 and HEK-293 transfected with flag-tuberin[16]. Moreover, high glucose has shown to phosphorylate tuberin in renal cells[13].

Tuberin, which is the product of tumor suppressor gene, *TSC-2*[17] normally, exists in an active state physically bound to hamartin, the product of *TSC-1* gene to form a stable complex[18]. These two proteins function within the same mTOR signaling pathway. mTOR is a serine/threonine kinase involved in numerous cell processes linked to cell growth control, like cell cycle progression, transcription and translation control as well as nutrient uptake[19]. Loss of *TSC-2* function either by *TSC-2* or *TSC-1* deficiency leads to constitutive activation of mTOR and downstream signaling pathways due to increased levels of GTP-bound Rheb[20-23]. Therefore tuberin, through its Rheb-GAP activity, is a critical negative regulator of mTOR under physiological conditions[24,25]. mTOR phosphorylates p70S6K (p70 ribosomal protein S6 kinase) on Thr389, which correlates with the activation of p70S6kinase[24-26], while over-expression of TSC-2 suppresses phosphorylation and activation of p70S6K on residue Thr389[14-16]. In addition, several studies have shown that Akt/mTOR pathway is activated in diabetes and this activation is redox dependent in different cell types[27-29] including renal cells[13].

Previous reports have shown that the serine/threonine kinase, mTOR to be involved in the phosphorylation/inactivation of Bcl-2 in microtubules treated with apoptotic agents[30]. Bcl-2 plays a central role in monitoring the genetic programs of the organism[31,32]. Bcl2 related proteins comprise a family of positive and negative regulators of apoptosis. Bcl-2 and its close homolog Bcl-XL are anti-apoptotic, whereas other members of the Bcl-2 family, such as BAD or BAX are proapoptotic[33]. Bcl-2 has been shown to prevent the release of cytochrmoe C from mitochondria and hence activation of caspase 9, the initiator caspase[32]. Several kinases like JNK, p38[33] and cdc2/cyclin B kinase[34] have been noticed to phosphorylate/inactivate Bcl-2 as a physiological process during normal cell cycle progression or as a defense mechanism following the activation by various stimuli and stress. Phosphorylation/inactivation of Bcl-2 inactivates the antiapoptotic effect, which triggers the release of cytochrome C from the mitochondria leading to the activation of downstream caspases[35-37].

Another important protein involved in apoptosis is

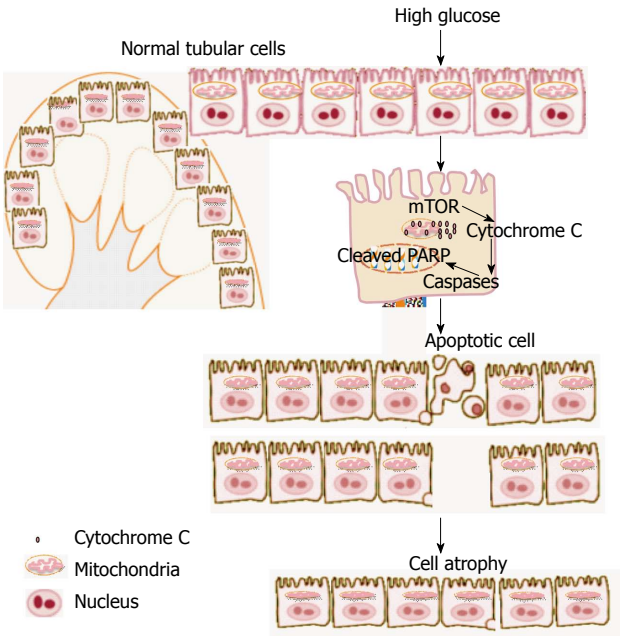

Figure 1 Proposed model of induction of cell apoptosis and subsequent of cell atrophy by high glucose in kidney.

poly (ADP-Ribose) polymerase (PARP), a DNA repair enzyme that is cleaved by the downstream caspases. The essential role of PARP activation in diabetes induced by streptozotocin in adult male BALB/c mice[38]. PARP catalyzes the poly(ADP-ribosyl)ation of a variety of nuclear proteins with NAD substrate. Because it is activated by binding to DNA ends or strand breaks, an important feature of the cell in apoptosis, PARP was suggested to contribute to apoptosis by depleting the cell of NAD and ATP[39]. When PARP is cleaved into 89- and 24-kDa fragments that contain the active site and the DNA binding domain of the enzyme, respectively during drug induced apoptosis in a variety of cells[39]. Such cleavage essentially inactivates the enzyme by destroying its ability to respond to DNA strand breaks/fragmentation.

Proteases play a critical role in the initiation and execution of apoptosis. The caspases, a family of cysteine-dependent, aspartate-directed proteases, are prominent among apoptosis-associated molecules[40]. Activation of caspases cleaves a variety of intracellular polypeptides, including major structural elements of the cytoplasm and nucleus, components of DNA repair machinery and a number of protein kinases. Caspase 3, a member of the caspase family plays a central role in the execution of the apoptotic program[41-43]. Oxidative stress mediated activation of caspase 3 has been shown to be a principle mediator of hyperglycemia induced proximal tubular apoptosis[5]. Caspase 3 is primarily responsible for the cleavage of PARP during cell death[41-45]. Recent published data show that high glucose and hyperglycemia induced cell apoptosis mainly in proximal tubular cells through regulation Bcl2/caspase/PARP pathway[46-49]. The sequence at which caspase 3 cleave PARP is very well conserved in the PARP protein from very distant species, indicating

the potential importance of PARP cleavage in apoptosis. Recent study from our lab showed the important role of tuberin/mTOR pathway in regulation of apoptosis[50]. We showed that induction of diabetes increased phosphorylation of tuberin in association with mTOR activation (measured by p70S6K phosphorylation), inactivation of Bcl-2, increased cytosolic cytochrome c expression, activation of caspase 3, and cleavage of PARP; insulin treatment prevented these changes. In addition, exposure of proximal tubular epithelial cells to high glucose increased phosphorylation of tuberin and p70S6K, phosphorylation of Bcl-2, expression of cytosolic cytochrome c, and caspase 3 activity. Moreover, high glucose induced translocation of the caspase substrate YY1 from the cytoplasm to the nucleus and enhanced cleavage of PARP. Cells treated with the mTOR inhibitor rapamycin resulted in reduce the number of apoptotic cells induced by high glucose[50]. This signaling cascade may play an important role in apoptosis induced by hyperglycemia during diabetic nephropathy. In summary, tubular apoptosis is one of the characteristic morphologic changes in human diabetic kidneys and tubular atrophy appears to be a better indicator of disease progression than glomerular pathology. A proposed model of induction of cell apoptosis and subsequent of cell atrophy by high glucose in kidney show in Figure 1. The mechanism by which hyperglycemia regulates apoptosis in renal tubular cells requires further study to provide the optimal management for diabetic complications.

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